UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,799	11/12/2003	Ilan Kor	1662/53605	7835

26646 7590 05/25/2007

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	**PAPER NUMBER**
1626	
MAIL DATE	**DELIVERY MODE**
05/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/712,799	KOR ET AL.	
	Examiner	Art Unit	
	Rebecca L. Anderson	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 17-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 17-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10 and 17-21 are currently pending in the instant application and are rejected.

Response to Amendment

Applicants' amendment to the claims has overcome the 35 USC 112 2nd paragraph rejection of claims 4, 6 and 9.

Applicants' amendment to the claims has overcome the 35 USC 112 2nd paragraph rejection of claims 1-10 and 17-21 for including a "solvate", however, as stated on page 4 of the specification, a solvate of Form VI has the disclosed X-ray diffraction pattern, the FTIR, and the DSC thermogram, therefore the claims are now rejected under 35 USC 112 1st paragraph as containing new matter as Form VI does not have the claimed X-ray, FTIR or DSC thermogram as the data provided in the claims is for a specific solvate only and not the unsolvated Form VI.

Response to Arguments

Applicant's arguments filed 6 March 2007 have been fully considered.

The objection to claims 2-10 and 17 as being duplicate claims is withdrawn in view of applicants' arguments.

In regards to the 35 USC 112 1st paragraph rejection of claims 18-21 applicants argue that the evidence cited is inadequate. While the specification teaches that carvedilol Form VI can be formulated into pharmaceutical compositions, the specification does not provide any evidence or showing that the pharmaceutical composition prepared contains Form VI. The specification does not teach that Form VI

will persist after being formulated into a pharmaceutical composition. The evidence to rebut that Form VI will persist after being formulated is adequate and is that Rouhi discloses that the art is well aware of the prospect of possible conversion of one crystalline form into another and that drug companies sometimes trade off polymorph stability with solubility recognizing that they will have to deal with the possibility of an undesired conversion to a more thermodynamically stable form. Applicant has not provided any evidence or disclosure of how undesired conversion was dealt with, nor has applicant provided any evidence of what form is found in the pharmaceutical compositions prepared. Additionally, it has been shown that the usual procedures for making pharmaceutical compositions, such as ball milling, grinding, and adding water will convert polymorphs to other forms. While Rouhi teaches that pharmaceutical companies are actively seeking new crystalline forms of compounds in order to formulate these new crystalline forms into pharmaceutical compositions, Rouhi does not teach that all pharmaceutical compositions and all methods of preparing pharmaceutical compositions would be able to maintain a new metastable form. Contrary, it is shown that ball milling, grinding and the addition of water will change the form. While US pharmacopia states that conversion can be quite slow and that several polymorphs of crystalline pharmaceutical compounds can exist under normal handling conditions, it is noted that while conversion "can" be quite slow, it is not stated to "be" slow, additionally, the preparation of pharmaceutical compounds can utilize conditions more harsh than normal handling conditions which can change the form. While applicant argues the pharmaceutical compositions do not contain solutions, it is noted that the claims do not

limit the composition to a solid but just that it comprises the crystalline solid of carvedilol and at least one pharmaceutically acceptable carrier, which can be water. Adding the crystalline solid of carvedilol to water will prepare a solution composition.

Applicant's arguments with respect to claims 1, 2, 5-10 and 17-21 have been considered but are moot in view of the new ground(s) of rejection of these claims under 35 USC 112 1st paragraph. The rejection of claims 1, 2, 5-10 and 17-21 as being indefinite is withdrawn.

In regards to the 35 USC 112 2nd paragraph rejection of claim 10, applicant argues that the bounds of claim 10 would be understood in light of the specification. This argument is not persuasive as Form VI is not a limiting element and does not define a difference in the carvedilol. Form VI is not a common well recognized term in the art to define anything. While Form VI is a term defined by the inventors, the definition found in the instant specification as the PXRD, DSC thermogram and FTIR spectrum data is for a solvate of Form VI, no data is present for Form VI.

In regards to the 35 USC 102 rejection of claims 1-10 and 17-21 as being anticipated applicants' arguments are persuasive and the rejections are withdrawn in regards to claims 1-9. However, the rejection is maintained for the pharmaceutical composition claims, which have not been demonstrated to be in Form VI in the instant specification. Additionally, as claim 10 has no limiting element to define a difference from any carvedilol, the anticipation rejections are maintained. Lastly, claim 17 is a product by process claim. The product, crystalline solid of carvedilol is found in each reference as even though product-by-process claims are limited by and defined by the

process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). Also see M.P.E.P. 2113.

In regards to the 35 USC 103(a) rejection of the claims as being obvious over CHEN, US Patent No. 4,503.067, EP 0918055, EP 0893440, WO 99/05105, WO 02/00216 or US Patent Pre-Grant Publication No. 2004152756, Applicant argues that the disclosure of crystalline forms of carvedilol are different from the presently claimed Form VI. This argument is not persuasive as it is well recognized by an artisan having ordinary skill in the field that X-ray diffraction while being able to show crystallinity does not provide chemical identity information. The Byrn reference clearly taught that X-ray diffraction pattern, especially powdered X-ray diffraction pattern includes artifacts such as preferred orientation, thus, just because there are some difference, without other confirmation, different X-ray alone is no proof of a new polymorph.

Applicant argues that the rejection relies on hindsight based on Applicants' disclosure that the claimed crystalline Form VI exists. This argument is not persuasive as every compound has different polymorphic forms and that in general the number of forms known for a given compound is proportional to the time and money spent in research on that compound. Therefore, the skilled artisan is well aware of obtaining

polymorphic forms is based on money and time and there is nothing unobvious about it (see Wikipedia).

Applicants argue that the motivation suffers from a lack of specificity and there is a lack of known methods to make Form VI. This argument is not persuasive as Grell et al. J. Med. Chem disclosed that in making the different crystalline forms, variations of solvents are operable (see page 5227 paragraph below table 2). The employment of different solvents in the crystallization process are art recognized conventional variation for obtaining different forms (see Grell J. Med. Chem. P. 5227). In absence of unexpected results it is conventionally taught that such different solvents may produce products with different physical properties which are innate to the product. One would be motivated to prepare the instantly claimed invention since it has long been the practice in the chemical and pharmaceutical arts to produce compounds in the form of crystals to secure a pure product. Further, changing the form, purity or other characteristic of an old product does not render the novel form patentable where the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art. In re Cofer, 148 U.S.P.Q. 268 (CCPA 1966). Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline forms of known compounds would have been suggested to one skilled in the art.

Applicant argues that there could be no motivation to prepare form VI since it did not exist and there could be no reasonable expectation of successfully producing Form VI when there was no known way of making Form VI. Applicant argues that the prior art does not teach which particular combination of solvents, time, temperature, etc. should

be chosen from among the vast number of possible combinations of such parameters in order to produce Form VI. This argument is not persuasive as Grell et al. J. Med. Chem disclosed that in making the different crystalline forms, variations of solvents are operable (see page 5227 paragraph below table 2). The employment of different solvents in the crystallization process are art recognized conventional variation for obtaining different forms (see Grell J. Med. Chem. P. 5227). In absence of unexpected results it is conventionally taught that such different solvents may produce products with different physical properties which are innate to the product. Additionally, this argument is not persuasive as every compound has different polymorphic forms and that in general the number of forms known for a given compound is proportional to the time and money spent in research on that compound. Therefore, the skilled artisan is well aware of obtaining polymorphic forms is based on money and time and there is nothing unobvious about it (see Wikipedia).

Applicant argues that the cases law of Deuel, O'Farrell, Obukowicz, In re Certain Crystalline Defadroxil Monohydrate, Cofer, Irani, Gala, Grose, and Papesch leads to the conclusion the rejection is in error.

Applicant argues that In re Deuel, 51 F. 3d 1552, 1559, 34 USPQ 2d 1210, 1216 (Fed. Cir. 1995) supports that a general incentive to look for additional crystalline forms once it is known that crystalline forms of a compound exist is not specific. This argument is not persuasive as more than general motivation is provided as Grell et al. J. Med. Chem disclosed that in making the different crystalline forms, variations of solvents are operable (see page 5227 paragraph below table 2). The

employment of different solvents in the crystallization process are art recognized conventional variation for obtaining different forms (see Grell J. Med. Chem. P. 5227). In absence of unexpected results it is conventionally taught that such different solvents may produce products with different physical properties which are innate to the product.

Applicant argues that In re O'Farrell, 853 F.2d 894, 903, 7 USPQ 2d 1673, 1681 (Fed Cir. 1988) and Ex parte Obukowixz, 27 USPQ 2d 1063, 1065 (Bd. Pat. App & Int. 1992) provide that the examiner's argument is merely "obvious to try". This argument is not persuasive as the prior art gives indications of which parameters are critical and direction as to which of the possible choices are likely to be successful as Grell et al. J. Med. Chem disclosed that in making the different crystalline forms, variations of solvents are operable (see page 5227 paragraph below table 2). The employment of different solvents in the crystallization process are art recognized conventional variation for obtaining different forms (see Grell J. Med. Chem. P. 5227). In absence of unexpected results it is conventionally taught that such different solvents may produce products with different physical properties which are innate to the product.
Even if the product of the instant application and the prior art may differ in X-ray diffraction or "form" the mere difference in physical parameter such as X-ray diffraction pattern does not offer any unexpected advantage of prior art product with the same chemical property and biological property.

Applicant argues that In re Certain Crystalline Cefadroxil Monohydrate provides that the motivation is general and would not direct to the particular claimed crystalline form. This argument is not persuasive as more than general motivation is provided as

Grell et al. J. Med. Chem disclosed that in making the different crystalline forms, variations of solvents are operable (see page 5227 paragraph below table 2). The employment of different solvents in the crystallization process are art recognized conventional variation for obtaining different forms (see Grell J. Med. Chem. P. 5227). In absence of unexpected results it is conventionally taught that such different solvents may produce products with different physical properties which are innate to the product.

Applicant argues that In re Cofer, 354 F.2d 664, 148 USPQ 268 (CCPA 1966) supports the Applicants' position that the claimed form is not obvious. This argument is not persuasive as the prior art gives indications of which parameters are critical and direction as to which of the possible choices are likely to be successful as Grell et al. J. Med. Chem disclosed that in making the different crystalline forms, variations of solvents are operable (see page 5227 paragraph below table 2). The employment of different solvents in the crystallization process are art recognized conventional variation for obtaining different forms (see Grell J. Med. Chem. P. 5227). In absence of unexpected results it is conventionally taught that such different solvents may produce products with different physical properties which are innate to the product. Even if the product of the instant application and the prior art may differ in X-ray diffraction or "form" the mere difference in physical parameter such as X-ray diffraction pattern does not offer any unexpected advantage of prior art product with the same chemical property and biological property.

Applicant argues that In re Irani, 427 F.2d 806, 166 USPQ 24 (CCPA 1970) supports Applicants' position. However, this argument is not persuasive as In re Irani is

based upon a non-crystalline form of the same compound. The prior art references are all crystalline forms of the same chemical compound.

Applicant argues that In re Grose, 592 F.2d 1161, 201 USPQ 57 (CCPA 1979) supports applicants' position that the lack of disclosure of a method of making the claimed crystalline Form VI in the prior art leads to a conclusion of non-obviousness as the conclusion of obviousness of one compound based upon its structural similarity to another compound depends upon the assumption that the method disclosed for producing the prior art compound can be used to produce the new compound. This argument is not persuasive as it is well recognized by an artisan having ordinary skill in the field that X-ray diffraction while being able to show crystallinity does not provide chemical identity information. The Byrn reference clearly taught that X-ray diffraction pattern, especially powdered X-ray diffraction pattern includes artifacts such as preferred orientation, thus, just because there are some difference, without other confirmation, different X-ray alone is no proof of a new polymorph. Additionally, Grell et al. J. Med. Chem disclosed that in making the different crystalline forms, variations of solvents are operable (see page 5227 paragraph below table 2). The employment of different solvents in the crystallization process are art recognized conventional variation for obtaining different forms (see Grell J. Med. Chem. P. 5227). In absence of unexpected results it is conventionally taught that such different solvents may produce products with different physical properties which are innate to the product.

Applicant argues that Ex parte Gala, 2002 WL 851814 ((Board of Patent Appeals & Interferences, date unavailable) supports that the properties of a claimed chemical

compound must be taken into account when conducting an obviousness inquiry. Applicant refers to In re Papesch, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963). This argument is not persuasive as the forms provided in the prior art are the same pure substance in which the molecules have different arrangements, without a patentability basis of an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, preparation or synthesis, hydroscopicity, recovery or prevention of precipitation, etc. (see Brittain p. 2, 185) it is prima facie obvious over the known product. Additionally, this argument is not persuasive as it is well recognized by an artisan having ordinary skill in the field that X-ray diffraction while being able to show crystallinity does not provide chemical identity information. The Byrn reference clearly taught that X-ray diffraction pattern, especially powdered X-ray diffraction pattern includes artifacts such as preferred orientation, thus, just because there are some difference, without other confirmation, different X-ray alone is no proof of a new polymorph. Applicant has not provided that there are indeed structural differences, nor has applicant provided that these structural differences would result in different properties.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case, Claims 18-21 claim compositions comprising crystalline solid of carvedilol form VI, such as an oral dosage form of a tablet.

The nature of the invention

A pharmaceutical composition comprising Form VI carvedilol.

The state of the prior art

The state of the prior art is that the preparation of pharmaceutical compositions requires, for example, milling, adding, excipients, surfactants, etc. The process of preparing a pharmaceutical composition will cause a specific crystalline form, if in the

metastable state to resort back to the most thermodynamically stable form, which is the form with the lowest vapor pressure. Polymorphs tend to convert from less stable to more stable forms (Rouhi, page 32). It is also the state of the art that an acceptable carrier for a pharmaceutical formulation, such as a suspension, can be water. Dissolving a specific crystalline form in water would put the compound in its free form and not any specific crystalline form. The use of a wrong polymorph of a drug when using an aqueous vehicle may provide a phase conversion from the metastable to stable polymorph (Haleblian et al. page 912).

The predictability or lack thereof in the art

The predictability or lack thereof in the art is that a metastable compound will resort back into its most thermodynamically stable form which would have a different X-ray diffraction pattern. Also, a solution prepared from a specific crystalline form and water would contain the free form of the compound.

The amount of direction or guidance present and the presence or absence of working examples

While the specification has provided processes for the preparation of the crystalline form VI, the specification does not provide examples of processes for preparing pharmaceutical compositions utilizing the crystalline form VI. The specification fails to provide the steps of ensuring that the pharmaceutical compositions will maintain the specific forms as found in the specification and will not resort back to the free form or the most thermodynamically stable form of the compound.

The breadth of the claims

A pharmaceutical composition comprising Form VI carvedilol.

The quantity of experimentation needed

The quantity of experimentation needed is undue. One of ordinary skill in the art, without direction, would be unable to maintain a specific metastable crystalline form upon preparation into a pharmaceutical composition which may require milling or formation of a solution at some time during the process of preparing the composition.

The level of the skill in the art

While the level of skill in the art is high, one of skill in the art would be unable to maintain a specific metastable crystalline form upon the preparation of a pharmaceutical composition without direction and guidance which is not found in the instant specification. One of skill in the art would expect the pharmaceutical composition to contain the most thermodynamically stable form of the compound or the free form of the compound.

Claims 1-10 and 17-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The nature of the invention is carvedilol Form VI. The state of the prior art is that the most useful method to compare X-ray powder diffraction data is to overlay and align the respective films or plots. The ensuing comparisons of peak positions and intensities will show whether the structures are the same or different (Byrn page 63). An x-ray diffraction pattern is like a "fingerprint" and applicant has not provided why the certain peaks found in the claims are the only required peaks in the x-ray diffraction pattern that must match. The peaks

present in the claims 1-3, 5-10 and 17-21 do not include all peaks of the x-ray diffraction pattern, nor does the specification provide any direction or guidance as to why certain peaks are the only required peaks in the x-ray data or other data. The claims 1-3, 5-10 and 17-21 are only drawn to certain peaks which is not the entire "fingerprint". The amount of direction present in the specification is the x-ray of form VI solvate. Page 4 discloses the data for a solvate of Form VI. Applicant has not provided why the entire "fingerprint" is not being claimed, nor does applicant provide why only certain peaks are found in the claims and not others. The claims to only certain peaks do not find written description in the specification as the claims do not include the enter "fingerprint" and the specification fails to provide any description as to why the data claimed is characteristic of Form VI and why the entire "fingerprint" is not required. Therefore the claims are rejected as there is no written description as to why the data present is the only data required from the "fingerprints" to distinguish Form VI from other forms. Additionally, the claim(s) 1-10 and 17-21 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the claims are drawn to Form VI with certain X-ray, DSC and FTIR data, however, the specification provides on page 4 that the data provided in the claims is for a solvate of Form VI and not Form VI itself. There is no support in the originally filed disclosure for Form VI with the claimed X-ray, DSC and FTIR data.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In regards to the chemical name of the carvedilol Form VI, it is noted that while the inventor may be his/her own lexicographer, claim 10 does not contain any of the physical data that particularly points out and distinctly claims the product that Applicant regards as his invention. Form VI is not a limiting element and does not define a difference in the carvedilol. Form VI is not a common well recognized term in the art to define anything. While Form VI is a term defined by the inventors, the definition found in the instant specification as the PXRD, DSC thermogram and FTIR spectrum data is for a solvate of Form VI, no data is present for Form VI. It is data that distinguishes applicants' invention from the prior art and not the term Form VI. For example, without PXRD data in the claim 10, it is impossible to distinguish applicants Form VI from any other crystalline carvedilol of the prior art, since there is no data in the claims to distinguish applicants' crystalline form any other crystalline form of the compound.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by CHEN, Wei Min et al.

CHEN, Wei Min et al. discloses crystalline carvedilol on page 325 and in figure 1, page 328.

Claims 10 and 17-21 are rejected under 35 USC 102(b) as being anticipated by US Patent No. 4,503,067.

US Patent No. 4,503,067 discloses pharmaceutical compositions on column 4, for example, in tablets. Example 2, column 5 discloses crystalline carvedilol which is obtained from recrystallization with ethyl acetate.

Claims 10 and 17-19 are rejected under 35 USC 102(b) as being anticipated by EP 0918055.

EP 0918055 discloses pharmaceutical use on page 2 as a drug having antihypertrensive activity. Examples 6 and 7 and 8, pages 111, disclose crystalline carvedilol which is recrystallized from ethyl acetate.

Claims 10, 17 and 18-21 are rejected under 35 USC 102(b) as being anticipated by EP 0893440.

EP 0893440 discloses carvedilol of form I and II on page 3. Pharmaceutical compositions are disclosed on pages 2 and 3, such as tablets, along with in claim 6, see page 4.

Claims 10, 17 and 18-21 are rejected under 35 USC 102(b) as being anticipated by WO 99/05105.

WO 99/05105 discloses carvedilol of form I and II on pages 5 and 6. Pharmaceutical compositions are disclosed on page 4, such as tablets, along with in claim 6, page 9.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 10, 17 and 18-21 are rejected under 35 U.S.C. 102 (a) and (e) as being anticipated by WO 02/00216.

WO 02/00216 discloses crystalline carvedilol of form III, IV and V and the solvate of methyl-ethyl-ketone) on pages 5, 15 and 16. Pharmaceutical compositions containing carvedilol are disclosed on pages 17-18, such as tablets.

Claims 10, 17 and 18-19 are rejected under 35 USC 102(e) as being anticipated by US Pre-Grant Publication No. 2004152756.

US Pre-Grant Publication No. 2004152756 discloses crystalline carvedilol form III and pharmaceutical compositions on page 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over CHEN, Wei-Min et al. in view of Grell et al. or Byrn.

Determining the scope and contents of the prior art

CHEN, Wei Min et al. discloses crystalline carvedilol on page 325 and in figure 1, page 328.

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the instant claims is that the X-ray diffraction pattern the crystalline solid of the prior art may differ from that of the X-ray diffraction pattern of the instant claims.

Resolving the level of ordinary skill in the pertinent art

However, it would have been obvious to one of ordinary skill in the art when faced with CHEN to prepare applicants' instantly claimed product as Grell et al. J. Med. Chem disclosed that in making the different crystalline forms, variations of solvents are

operable (see page 5227 paragraph below table 2). The employment of different solvents in the crystallization process are art recognized conventional variation for obtaining different forms (see Grell J. Med. Chem. P. 5227). In absence of unexpected results it is conventionally taught that such different solvents may produce products with different physical properties which are innate to the product. Even if the product of the instant application and the prior art may differ in X-ray diffraction or "form" the mere difference in physical parameter such as X-ray diffraction pattern does not offer any unexpected advantage of prior art product with the same chemical property and biological property. Additionally, it is well recognized by an artisan having ordinary skill in the field that X-ray diffraction while being able to show crystallinity does not provide chemical identity information. The Byrn reference clearly taught that X-ray diffraction pattern, especially powdered X-ray diffraction pattern includes artifacts such as preferred orientation, thus, just because there are some difference, without other confirmation, different X-ray alone is no proof of a new polymorph. One would be motivated to prepare the instantly claimed invention since it has long been the practice in the chemical and pharmaceutical arts to produce compounds in the form of crystals to secure a pure product. Further, changing the form, purity or other characteristic of an old product does not render the novel form patentable where the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art. In re Cofer, 148 U.S.P.Q. 268 (CCPA 1966). Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline forms of known compounds would have been suggested to one skilled in the art.

Claims 1-10 and 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 4,503,067 in view of Grell et al. or Byrn.

Determining the scope and contents of the prior art

US Patent No. 4,503,067 discloses Example 2, column 5 which discloses crystalline carvedilol which is obtained from recrystallization with ethyl acetate.

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the instant claims is that the X-ray diffraction pattern the crystalline solid of the prior art may differ from that of the X-ray diffraction pattern of the instant claims.

Resolving the level of ordinary skill in the pertinent art

However, it would have been obvious to one of ordinary skill in the art when faced with US Patent No. 4,503,067 to prepare applicants' instantly claimed product as Grell et al. J. Med. Chem disclosed that in making the different crystalline forms, variations of solvents are operable (see page 5227 paragraph below table 2). The employment of different solvents in the crystallization process are art recognized conventional variation for obtaining different forms (see Grell J. Med. Chem. P. 5227). In absence of unexpected results it is conventionally taught that such different solvents may produce products with different physical properties which are innate to the product. Even if the product of the instant application and the prior art may differ in X-ray diffraction or "form" the mere difference in physical parameter such as X-ray diffraction pattern does not offer any unexpected advantage of prior art product with the same chemical property and biological property. Additionally, it is well recognized by an

artisan having ordinary skill in the field that X-ray diffraction while being able to show crystallinity does not provide chemical identity information. The Byrn reference clearly taught that X-ray diffraction pattern, especially powdered X-ray diffraction pattern includes artifacts such as preferred orientation, thus, just because there are some difference, without other confirmation, different X-ray alone is no proof of a new polymorph. One would be motivated to prepare the instantly claimed invention since it has long been the practice in the chemical and pharmaceutical arts to produce compounds in the form of crystals to secure a pure product. Further, changing the form, purity or other characteristic of an old product does not render the novel form patentable where the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art. In re Cofer, 148 U.S.P.Q. 268 (CCPA 1966). Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline forms of known compounds would have been suggested to one skilled in the art.

Claims 1-10 and 17-19 are rejected under 35 USC 103(a) as being unpatentable over EP 0918055 in view of Grell et al. or Byrn.

Determining the scope and contents of the prior art

EP 0918055 discloses Examples 6 and 7 and 8, pages 111, which disclose crystalline carvedilol which is recrystallized from ethyl acetate.

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the instant claims is that the X-ray diffraction pattern the crystalline solid of the prior art may differ from that of the X-ray diffraction pattern of the instant claims.

Resolving the level of ordinary skill in the pertinent art

However, it would have been obvious to one of ordinary skill in the art when faced with EP 0918055 to prepare applicants' instantly claimed product as Grell et al. J. Med. Chem disclosed that in making the different crystalline forms, variations of solvents are operable (see page 5227 paragraph below table 2). The employment of different solvents in the crystallization process are art recognized conventional variation for obtaining different forms (see Grell J. Med. Chem. P. 5227). In absence of unexpected results it is conventionally taught that such different solvents may produce products with different physical properties which are innate to the product. Even if the product of the instant application and the prior art may differ in X-ray diffraction or "form" the mere difference in physical parameter such as X-ray diffraction pattern does not offer any unexpected advantage of prior art product with the same chemical property and biological property. Additionally, it is well recognized by an artisan having ordinary skill in the field that X-ray diffraction while being able to show crystallinity does not provide chemical identity information. The Byrn reference clearly taught that X-ray diffraction pattern, especially powdered X-ray diffraction pattern includes artifacts such as preferred orientation, thus, just because there are some difference, without other confirmation, different X-ray alone is no proof of a new polymorph. One would be motivated to prepare the instantly claimed invention since it has long been the practice in the chemical and pharmaceutical arts to produce compounds in the form of crystals to secure a pure product. Further, changing the form, purity or other characteristic of an old product does not render the novel form patentable where the difference in form,

purity or characteristic was inherent in or rendered obvious by the prior art. In re Cofer, 148 U.S.P.Q. 268 (CCPA 1966). Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline forms of known compounds would have been suggested to one skilled in the art.

Claims 1-10 and 17-21 are rejected under 35 USC 103(a) as being unpatentable over EP 0893440 in view of Grell et al. or Byrn.

Determining the scope and contents of the prior art

EP 0893440 discloses carvedilol of form I and II on page 3.

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the instant claims is that the X-ray diffraction pattern the crystalline solid of the prior art may differ from that of the X-ray diffraction pattern of the instant claims.

Resolving the level of ordinary skill in the pertinent art

However, it would have been obvious to one of ordinary skill in the art when faced with EP 0893440 to prepare applicants' instantly claimed product as Grell et al. J. Med. Chem disclosed that in making the different crystalline forms, variations of solvents are operable (see page 5227 paragraph below table 2). The employment of different solvents in the crystallization process are art recognized conventional variation for obtaining different forms (see Grell J. Med. Chem. P. 5227). In absence of unexpected results it is conventionally taught that such different solvents may produce products with different physical properties which are innate to the product. Even if the product of the instant application and the prior art may differ in X-ray diffraction or "form"

the mere difference in physical parameter such as X-ray diffraction pattern does not offer any unexpected advantage of prior art product with the same chemical property and biological property. Additionally, it is well recognized by an artisan having ordinary skill in the field that X-ray diffraction while being able to show crystallinity does not provide chemical identity information. The Byrn reference clearly taught that X-ray diffraction pattern, especially powdered X-ray diffraction pattern includes artifacts such as preferred orientation, thus, just because there are some difference, without other confirmation, different X-ray alone is no proof of a new polymorph. One would be motivated to prepare the instantly claimed invention since it has long been the practice in the chemical and pharmaceutical arts to produce compounds in the form of crystals to secure a pure product. Further, changing the form, purity or other characteristic of an old product does not render the novel form patentable where the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art. In re Cofer, 148 U.S.P.Q. 268 (CCPA 1966). Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline forms of known compounds would have been suggested to one skilled in the art.

Claims 1-10 and 17-21 are rejected under 35 USC 103(a) as being unpatentable over WO 99/05105 in view of Grell et al. or Byrn.

Determining the scope and contents of the prior art

WO 99/05105 discloses carvedilol of form I and II on pages 5 and 6.

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the instant claims is that the X-ray diffraction pattern the crystalline solid of the prior art may differ from that of the X-ray diffraction pattern of the instant claims.

Resolving the level of ordinary skill in the pertinent art

However, it would have been obvious to one of ordinary skill in the art when faced with WO 99/05105 to prepare applicants' instantly claimed product as Grell et al. J. Med. Chem disclosed that in making the different crystalline forms, variations of solvents are operable (see page 5227 paragraph below table 2). The employment of different solvents in the crystallization process are art recognized conventional variation for obtaining different forms (see Grell J. Med. Chem. P. 5227). In absence of unexpected results it is conventionally taught that such different solvents may produce products with different physical properties which are innate to the product. Even if the product of the instant application and the prior art may differ in X-ray diffraction or "form" the mere difference in physical parameter such as X-ray diffraction pattern does not offer any unexpected advantage of prior art product with the same chemical property and biological property. Additionally, it is well recognized by an artisan having ordinary skill in the field that X-ray diffraction while being able to show crystallinity does not provide chemical identity information. The Byrn reference clearly taught that X-ray diffraction pattern, especially powdered X-ray diffraction pattern includes artifacts such as preferred orientation, thus, just because there are some difference, without other confirmation, different X-ray alone is no proof of a new polymorph. One would be motivated to prepare the instantly claimed invention since it has long been the practice

in the chemical and pharmaceutical arts to produce compounds in the form of crystals to secure a pure product. Further, changing the form, purity or other characteristic of an old product does not render the novel form patentable where the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art. In re Cofer, 148 U.S.P.Q. 268 (CCPA 1966). Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline forms of known compounds would have been suggested to one skilled in the art.

Claims 1-10 and 17-21 are rejected under 35 USC 103(a) as being unpatentable over WO 02/00216 in view of Grell et al. or Byrn.

Determining the scope and contents of the prior art

WO 02/00216 discloses crystalline carvedilol of form III, IV and V and the solvate of methyl-ethyl-ketone) on pages 5, 15 and 16.

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the instant claims is that the X-ray diffraction pattern the crystalline solid of the prior art may differ from that of the X-ray diffraction pattern of the instant claims.

Resolving the level of ordinary skill in the pertinent art

However, it would have been obvious to one of ordinary skill in the art when faced with WO 02/00216 to prepare applicants' instantly claimed product as Grell et al. J. Med. Chem disclosed that in making the different crystalline forms, variations of solvents are operable (see page 5227 paragraph below table 2). The employment of different solvents in the crystallization process are art recognized conventional variation

for obtaining different forms (see Grell J. Med. Chem. P. 5227). In absence of unexpected results it is conventionally taught that such different solvents may produce products with different physical properties which are innate to the product. Even if the product of the instant application and the prior art may differ in X-ray diffraction or "form" the mere difference in physical parameter such as X-ray diffraction pattern does not offer any unexpected advantage of prior art product with the same chemical property and biological property. Additionally, it is well recognized by an artisan having ordinary skill in the field that X-ray diffraction while being able to show crystallinity does not provide chemical identity information. The Byrn reference clearly taught that X-ray diffraction pattern, especially powdered X-ray diffraction pattern includes artifacts such as preferred orientation, thus, just because there are some difference, without other confirmation, different X-ray alone is no proof of a new polymorph. One would be motivated to prepare the instantly claimed invention since it has long been the practice in the chemical and pharmaceutical arts to produce compounds in the form of crystals to secure a pure product. Further, changing the form, purity or other characteristic of an old product does not render the novel form patentable where the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art. In re Cofer, 148 U.S.P.Q. 268 (CCPA 1966). Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline forms of known compounds would have been suggested to one skilled in the art.

Claims 1-10 and 121 are rejected under 35 USC 103(a) as being unpatentable over US Pre-Grant Publication No. 2004152756 in view of Grell et al. or Byrn.

Determining the scope and contents of the prior art

US Pre-Grant Publication No. 2004152756 discloses crystalline carvedilol form III on page 1.

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the instant claims is that the X-ray diffraction pattern the crystalline solid of the prior art may differ from that of the X-ray diffraction pattern of the instant claims.

Resolving the level of ordinary skill in the pertinent art

However, it would have been obvious to one of ordinary skill in the art when faced with US Pre-Grant Publication No. 2004152756 to prepare applicants' instantly claimed product as Grell et al. J. Med. Chem disclosed that in making the different crystalline forms, variations of solvents are operable (see page 5227 paragraph below table 2). The employment of different solvents in the crystallization process are art recognized conventional variation for obtaining different forms (see Grell J. Med. Chem. P. 5227). In absence of unexpected results it is conventionally taught that such different solvents may produce products with different physical properties which are innate to the product. Even if the product of the instant application and the prior art may differ in X-ray diffraction or "form" the mere difference in physical parameter such as X-ray diffraction pattern does not offer any unexpected advantage of prior art product with the same chemical property and biological property. Additionally, it is well recognized by an artisan having ordinary skill in the field that X-ray diffraction while being able to show crystallinity does not provide chemical identity information. The Byrn reference clearly

taught that X-ray diffraction pattern, especially powdered X-ray diffraction pattern includes artifacts such as preferred orientation, thus, just because there are some difference, without other confirmation, different X-ray alone is no proof of a new polymorph. One would be motivated to prepare the instantly claimed invention since it has long been the practice in the chemical and pharmaceutical arts to produce compounds in the form of crystals to secure a pure product. Further, changing the form, purity or other characteristic of an old product does not render the novel form patentable where the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art. In re Cofer, 148 U.S.P.Q. 268 (CCPA 1966). Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline forms of known compounds would have been suggested to one skilled in the art.

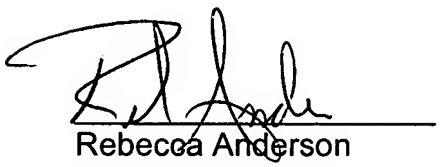
Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



24 May 2007

Rebecca Anderson
Primary Examiner
Art Unit 1626, Group 1620
Technology Center 1600